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Research Article

Modeling TB-HIV Syndemic and Treatment

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Tuberculosis (TB) and human immunodeficiency virus (HIV) can be considered a deadly human syndemic. In this paper, we formulate a model for TB and HIV transmission dynamics. The model considers both TB and acquired immune deficiency syndrome (AIDS) treatment for individuals with only one of the two infectious diseases or both. The basic reproduction number and equilibrium points are determined and stability is analyzed. Through simulations, we show that TB treatment for individuals with only TB infection reduces the number of individuals that become coinfected with TB and HIV/AIDS and reduces the diseases (TB and AIDS) induced deaths. Analogously, the treatment of individuals with only AIDS also reduces the number of coinfected individuals. Further, TB treatment for coinfected individuals in the active and latent stage of TB disease implies a decrease of the number of individuals that passes from HIV-positive to AIDS.

1. Introduction

Tuberculosis (TB) and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) are the leading causes of death from an infectious disease worldwide [1]. Individuals infected with HIV are more likely to develop TB disease because of their immunodeficiency, and HIV infection is the most powerful risk factor for progression from TB infection to disease [2]. This interaction justifies the fact that HIV and TB can be considered a deadly human *syndemic*, where syndemic refers to the convergence of two or more diseases that act synergistically to magnify the burden of disease [3].

Following UNAIDS global report on AIDS epidemic 2013 [4], globally, an estimated 35.3 million people were living with HIV in 2012, an increase from previous years as more people are receiving the life-saving antiretroviral therapy (ART). There were approximately 2.3 million new HIV infections globally, showing a 33% decline in the number of new infections with respect to 2001. At the same time, the number of AIDS deaths is also declining with around 1.6 million AIDS deaths in 2012, down from about 2.3 million in 2005. In 2012, 1.1 million of 8.6 million people who developed TB worldwide were HIV-positive. The number of people dying from HIV-associated TB has been falling since 2003. However, there were still 320 000 deaths from HIV-associated TB in 2012 and further efforts are needed to reduce this burden [1]. ART is a critical intervention for reducing the risk of TB morbidity and mortality among people living with HIV and, when combined with isoniazid preventive therapy, it can have a significant impact on TB prevention [1].

Collaborative TB/HIV activities (including HIV testing, ART therapy, and TB preventive measures) are crucial for the reduction of TB-HIV coinfected individuals. The World Health Organization (WHO) estimates that these collaborative activities prevented 1.3 million people from dying, from 2005 to 2012. However, significant challenges remain: the reduction of tuberculosis related deaths among people living with HIV has slowed in recent years; the ART therapy is not being delivered to TB-HIV coinfected patients in the majority of the countries with the largest number of TB/HIV patients; the pace of treatment scale-up for TB/HIV patients has slowed; less than half of notified TB patients were tested for HIV in 2012; and only a small fraction of TB/HIV-infected individuals received TB preventive therapy [4].

The study of the joint dynamics of TB and HIV presents formidable mathematical challenges due to the fact that the models of transmission are quite distinct [5]. Few mathematical models have been proposed for TB-HIV coinfection (see, e.g., [5–9]). Kirschner [7] developed a cellular model

for HIV-1 and TB coinfection inside a host. Roeger et al. [5] proposed a population model for TB-HIV/AIDS coinfection transmission dynamics, assuming that TB-infected individuals in the active stage of the disease are too ill to remain sexually active and therefore they are unable to transmit HIV. In this work, we assume that active TB-infected individuals are susceptible to HIV infection. Naresh and Tripathi [8] proposed a model for TB-HIV coinfection in a variable size population with only TB treatment. Here we consider TB and HIV treatment in different stages of the disease. Bhunu et al. [6] studied a TB-HIV coinfection model with both TB and HIV treatment. The authors did not take into account that an individual coinfected with TB and HIV can effectively recover from TB infection. We assume that TB can be cured, even in HIV-positive individuals [1]. Sharomi et al. [9] also considered these assumptions, subdividing the total population into 15 classes. It is our aim in this work to develop a model that balances two goals: simplicity and useful information.

The paper is organized as follows. Section 2 describes our model for TB-HIV syndemic with TB and HIV treatment. In Section 3, the positivity and boundedness of solutions of the model are proved and in Section 4 equilibrium points and respective stability are analyzed. Section 5 is devoted to numerical simulations and discussion of results.

2. TB-HIV/AIDS Model

The model subdivides the human population into 10 mutually exclusive compartments, namely, susceptible individuals (S), TB-latently infected individuals, who have no symptoms of TB disease and are not infectious (L_T), TB-infected individuals, who have active TB disease and are infectious (I_T), TB-recovered individuals (R_T), HIV-infected individuals with no clinical symptoms of AIDS (I_H), HIV-infected individuals with AIDS clinical symptoms (A), TB-latent individuals coinfected with HIV (pre-AIDS) (L_{TH}), HIV-infected individuals (pre-AIDS) coinfected with active TB disease (I_{TH}), TB-recovered individuals with HIV infection without AIDS symptoms (R_{TH}), and HIV-infected individuals with AIDS symptoms coinfected with TB (A_T). The total population at time t, denoted by $N(t)$, is given by

$$\begin{aligned} N(t) = {} & S(t) + L_T(t) + I_T(t) + R_T(t) + I_H(t) + A(t) \\ & + I_{TH}(t) + L_{TH}(t) + R_{TH}(t) + A_T(t). \end{aligned} \tag{1}$$

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population, at a rate Λ. All individuals suffer from natural death, at a constant rate μ. Susceptible individuals acquire TB infection from individuals with active TB at a rate λ_T, given by

$$\lambda_T = \frac{\beta_1}{N}\left(I_T + I_{TH} + A_T\right), \tag{2}$$

where β_1 is the effective contact rate for TB infection. Similarly, susceptible individuals acquire HIV infection, following effective contact with people infected with HIV at a rate λ_H, given by

$$\lambda_H = \frac{\beta_2}{N}\left[I_H + I_{TH} + L_{TH} + R_{TH} + \eta\left(A + A_T\right)\right], \tag{3}$$

where β_2 is the effective contact rate for HIV transmission and the modification parameter $\eta \geqslant 1$ accounts for the relative infectiousness of individuals with AIDS symptoms, in comparison to those infected with HIV with no AIDS symptoms. Individuals with AIDS symptoms are more infectious than HIV-infected individuals (pre-AIDS) because they have a higher viral load and there is a positive correlation between viral load and infectiousness [14].

Individuals leave the latent TB class L_T by becoming infectious, at a rate k_1, or recovered, with a treatment rate τ_1. The treatment rate for active TB-infected individuals is τ_2. We assume that TB-recovered individuals R_T acquire partial immunity and the transmission rate for this class is given by $\beta_1'\lambda_T$ with $\beta_1' \leqslant 1$. Individuals with active TB disease suffer induced death at a rate d_T. We assume that individuals in the class R_T are susceptible to HIV infection at a rate λ_H. On the other hand, TB-active infected individuals I_T are susceptible to HIV infection, at a rate $\delta\lambda_H$, where the modification parameter $\delta \geqslant 1$ accounts for higher probability of individuals in class I_T to become HIV-positive.

HIV-infected individuals (with no AIDS symptoms) progress to the AIDS class A, at a rate ρ_1. HIV-infected individuals with AIDS symptoms are treated for HIV at the rate α_1 and suffer induced death at a rate d_A. Individuals in the class I_H are susceptible to TB infection at a rate $\psi\lambda_T$, where $\psi \geqslant 1$ is a modification parameter traducing the fact that HIV infection is a driver of TB epidemic [3].

HIV-infected individuals (pre-AIDS) coinfected with TB-disease, in the active stage I_{TH}, are treated for TB at the rate τ_3 and progress to the AIDS-TB coinfection class A_T at a rate ρ_2. Individuals in the class I_{TH} suffer TB induced death at a rate d_T. The anti-TB drugs can prevent or decrease the likelihood of TB infection progression to active TB disease in individuals in the class L_{TH} [13]. The treatment rate for individuals in this class is given by τ_4. However, individuals in the class L_{TH} are more likely to progress to active TB disease than individuals infected only with latent TB. In our model, this progression rate is given by k_2. Similarly, HIV infection makes individuals more susceptible to TB reinfection when compared with non-HIV-positive patients. The modification parameter associated with the TB reinfection rate, for individuals in the class R_{TH}, is given by β_2', where $\beta_2' \geqslant 1$. Individuals in this class progress to class A_T, at a rate ρ_3.

HIV-infected individuals (with AIDS symptoms), coinfected with TB, are treated for HIV, at a rate α_2. Individuals in the class A_T suffer from AIDS-TB coinfection induced death rate, at a rate d_{TA}.

The aforementioned assumptions result in the following system of differential equations that describes the transmission dynamics of TB and HIV disease:

$$\begin{aligned} \dot{S}(t) &= \Lambda - \lambda_T S(t) - \lambda_H S(t) - \mu S(t), \\ \dot{L}_T(t) &= \lambda_T S(t) + \beta_1'\lambda_T R_T(t) - \left(k_1 + \tau_1 + \mu\right) L_T(t), \\ \dot{I}_T(t) &= k_1 L_T(t) - \left(\tau_2 + d_T + \mu + \delta\lambda_H\right) I_T(t), \\ \dot{R}_T(t) &= \tau_1 L_T(t) + \tau_2 I_T(t) - \left(\beta_1'\lambda_T + \lambda_H + \mu\right) R_T(t), \end{aligned}$$

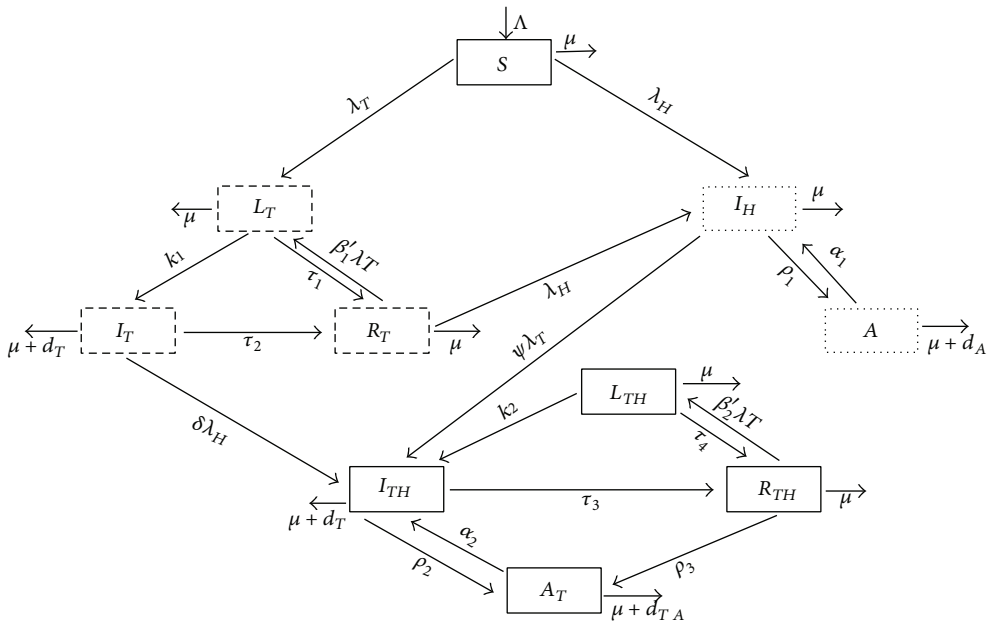

Figure 1: Model for TB-HIV/AIDS transmission with treatment.

$$\begin{aligned}
\dot{I}_H(t) &= \lambda_H S(t) - (\rho_1 + \psi\lambda_T + \mu) I_H(t) \\
&\quad + \alpha_1 A(t) + \lambda_H R_T(t), \\
\dot{A}(t) &= \rho_1 I_H(t) - \alpha_1 A(t) - (\mu + d_A) A(t), \\
\dot{L}_{TH}(t) &= \beta_2' \lambda_T R_{TH}(t) - (k_2 + \tau_4 + \mu) L_{TH}(t), \\
\dot{I}_{TH}(t) &= \delta\lambda_H I_T(t) + \psi\lambda_T I_H(t) + \alpha_2 A_T(t) \\
&\quad + k_2 L_{TH}(t) - (\tau_3 + \rho_2 + \mu + d_T) I_{TH}(t), \\
\dot{R}_{TH}(t) &= \tau_3 I_{TH}(t) + \tau_4 L_{TH}(t) - \left(\beta_2' \lambda_T + \rho_3 + \mu\right) R_{TH}, \\
\dot{A}_T(t) &= \rho_2 I_{TH}(t) + \rho_3 R_{TH} - (\alpha_2 + \mu + d_{TA}) A_T(t).
\end{aligned} \tag{4}$$

The model flow is described in Figure 1. The initial conditions of model (4) satisfy

$$\begin{aligned}
&S(0) = S_0 \geqslant 0, \qquad L_T(0) = L_{T0} \geqslant 0, \qquad I_T(0) = I_{T0} \geqslant 0, \\
&R_T(0) = R_{T0} \geqslant 0, \\
&I_H(0) = I_{H0} \geqslant 0, \qquad A(0) = A_0 \geqslant 0, \\
&L_{TH}(0) = L_{TH0} \geqslant 0, \\
&I_{TH}(0) = I_{TH0} \geqslant 0, \qquad R_{TH}(0) = R_{TH0} \geqslant 0, \\
&A_T(0) = A_{T0} \geqslant 0.
\end{aligned} \tag{5}$$

Note that if we consider the submodel of (4) with no HIV/AIDS disease, that is, $I_H = A = L_{TH} = I_{TH} = R_{TH} = A_T = 0$, then we obtain the TB model from [12]. On the other hand, if we consider the submodel with no TB, that is, $L_T = I_T = R_T = L_{TH} = I_{TH} = R_{TH} = A_T = 0$, then we obtain an HIV/AIDS model based on the models proposed in [6, 15].

3. Positivity and Boundedness of Solutions

Let $(S, L_T, I_T, R_T, I_H, A, L_{TH}, I_{TH}, R_{TH}, A_T) \in \mathbb{R}_+^{10}$ be any solution of (4) with initial conditions (5). Consider the biologically feasible region given by

$$\begin{aligned}
\Omega = \Bigg\{ &(S, L_T, I_T, R_T, I_H, A, L_{TH}, I_{TH}, R_{TH}, A_T) \\
&\in \mathbb{R}_+^{10} : 0 \leqslant N(t) \leqslant \frac{\Lambda}{\mu} \Bigg\}.
\end{aligned} \tag{6}$$

For the model system (4) to be epidemiologically meaningful, it is important to prove that all its state variables are nonnegative for all time $t > 0$. Suppose, for example, that at some $\bar{t} > 0$ the variable L_T becomes zero, that is, $L_T(\bar{t}) = 0$, while all other variables are positive. Then, from the L_T equation we have $dL_T(\bar{t})/dt > 0$. Thus, $L_T(t) \geqslant 0$ for all $t > 0$. Analogously, we can prove that all variables remain nonnegative for all time $t > 0$.

Adding all equations in model (4) gives

$$\begin{aligned}
\frac{dN}{dt}(t) &= \Lambda - \mu N(t) - d_T I_T(t) - d_A A(t) \\
&\quad - d_T I_{TH}(t) - d_{TA} A_T(t).
\end{aligned} \tag{7}$$

Since $N(t) \geqslant I_T(t) + A(t) + I_{TH}(t) + A_T(t)$, then

$$\Lambda - (\mu + d_T + d_A + d_{TA}) N(t) \leqslant \frac{dN}{dt}(t) \leqslant \Lambda - \mu N(t). \tag{8}$$

Therefore, we conclude that $N(t)$ is bounded for all $t > 0$ and every solution of system (4) with initial condition in Ω remains in Ω. This result is summarized below.

Lemma 1. *The region Ω is positively invariant for model (4) with nonnegative initial conditions in $\mathbb{R}^{10}_{+}$.*

4. Stability Analysis

Model (4) has four nonnegative equilibria, namely,

(i) the disease-free equilibrium (no disease):

$$\begin{aligned}\Sigma_0 &= \left(S_0, L_{T_0}, I_{T_0}, R_{T_0}, I_{H_0}, A_0, L_{TH_0}, I_{TH_0}, R_{TH_0}, A_{T_0}\right)\\ &= \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0\right),\end{aligned} \tag{9}$$

(ii) the HIV-AIDS free equilibrium:

$$\Sigma_T = \left(S^{\diamond}, L_T^{\diamond}, I_T^{\diamond}, R_T^{\diamond}, I_H^{\diamond}, A^{\diamond}, L_{TH}^{\diamond}, I_{TH}^{\diamond}, R_{TH}^{\diamond}, A_T^{\diamond}\right) \tag{10}$$

with $I_T^{\diamond} > 0$ and $I_H^{\diamond} = A^{\diamond} = L_{TH}^{\diamond} = I_{TH}^{\diamond} = R_{TH}^{\diamond} = A_T^{\diamond} = 0$ for $R_1 > 1$, where R_1 is the basic reproduction number of model (4) with $I_H = A = L_{TH} = I_{TH} = R_{TH} = A_T = 0$ (only TB model) that is given by

$$R_1 = \frac{\Lambda}{N\mu}\left(\frac{\beta_1}{d_T + \mu + \tau_2}\right)\left(\frac{k_1}{k_1 + \tau_1 + \mu}\right) \tag{11}$$

(see [12]),

(iii) the TB-free equilibrium:

$$\Sigma_H = \left(S^{\star}, L_T^{\star}, I_T^{\star}, R_T^{\star}, I_H^{\star}, A^{\star}, L_{TH}^{\star}, I_{TH}^{\star}, R_{TH}^{\star}, A_T^{\star}\right) \tag{12}$$

with $L_T^{\star} = I_T^{\star} = R_T^{\star} = L_{TH}^{\star} = I_{TH}^{\star} = R_{TH}^{\star} = A_T^{\star} = 0$ and

$$S^{\star} = \frac{\Lambda}{\mu R_2}, \tag{13}$$

$$I_H^{\star} = \left(R_2 - 1\right)\frac{\mu N_H\left(\alpha_1 + d_A + \mu\right)}{\beta_2\left(\alpha_1 + d_A + \mu + \eta\rho_1\right)}, \tag{14}$$

$$A^{\star} = \left(R_2 - 1\right)\frac{\rho_1\mu N_H}{\beta_2\left(\alpha_1 + d_A + \mu + \eta\rho_1\right)}, \tag{15}$$

for $R_2 > 1$, where R_2 is the basic reproduction number of model (4) with $L_T = I_T = R_T = L_{TH} = I_{TH} = R_{TH} = A_T = 0$ (only HIV-AIDS model); that is,

$$R_2 = \frac{\Lambda}{N\mu}\beta_2\left(\frac{\mu + \alpha_1 + d_A + \eta\rho_1}{\mu\alpha_1 + \left(\mu + \rho_1\right)\left(\mu + d_A\right)}\right), \tag{16}$$

(iv) the syndemic equilibrium:

$$\Sigma^{*} = \left(S^{*}, L_T^{*}, I_T^{*}, R_T^{*}, I_H^{*}, A^{*}, L_{TH}^{*}, I_{TH}^{*}, R_{TH}^{*}, A_T^{*}\right) \tag{17}$$

with $I_T^{*} > 0$, $I_H^{*} > 0$, $A^{*} > 0$, $L_{TH}^{*} > 0$, $I_{TH}^{*} > 0$, $R_{TH}^{*} > 0$, and $A_T^{*} > 0$, for $R_0 > 1$, where R_0 is the basic reproduction number of model (4); that is,

$$R_0 = \max\left\{R_1, R_2\right\}. \tag{18}$$

The details of the computation of the basic reproduction number R_0 are given in Appendix A.

The following theorem states the stability of the equilibrium points.

Theorem 2. *The disease-free equilibrium Σ_0 is locally asymptotically stable if $R_0 < 1$ and unstable if either $R_i > 1$ with $i = 1, 2$. The HIV-AIDS free equilibrium Σ_T is locally asymptotically stable if $R_1 > 1$, and the TB-free equilibrium Σ_H is locally asymptotically stable for R_2 near 1.*

Details of the proof of Theorem 2 are given in Appendix B.

Explicit expressions for the coinfection endemic equilibrium Σ^{*} are very difficult to compute analytically. In Section 5, we consider an example, with $R_0 > 1$, for which there exists a syndemic equilibrium, and analyze, numerically, the local asymptotical stability of the syndemic equilibrium Σ^{*}.

5. Numerical Analysis and Discussion

For numerical simulations, we consider the following initial conditions for system (4):

$$\begin{aligned}&\left(S(0), L_T(0), I_T(0), R_T(0), I_H(0), A(0),\right.\\ &\left.L_{TH}(0), I_{TH}(0), R_{TH}(0), A_T(0)\right)\\ &= \left(\frac{60N}{100}, \frac{14N}{100}, \frac{3N}{100}, 0, \frac{4N}{100}, \frac{N}{100}, \frac{12N}{100}, \frac{5N}{100}, 0, \frac{N}{100}\right)\end{aligned} \tag{19}$$

with $N = 50000$. The parameters of model (4) take the values of Table 1.

5.1. Equilibrium Points and Stability Analysis. In Table 2 we show the effect of the transmission coefficient β_1 on the state $I_T^{\diamond}$ of the HIV-free equilibrium Σ_T and on the basic reproduction number R_1. Table 3 shows the effect of the transmission coefficient β_2 on the states $I_H^{\star}$ and $A^{\star}$ of the TB-free equilibrium Σ_H and on the basic reproduction number R_2. We conclude that the equilibrium states $I_T^{\diamond}$ and $(I_H^{\star}, A^{\star})$ increase with the transmission coefficients β_1 and β_2, respectively.

In Figure 2 we considered different initial conditions in a neighborhood of the initial conditions given by (19) and $R_0 < 1$ ($R_1 < 1$ and $R_2 < 1$) to illustrate the stability of the disease-free equilibrium Σ_0 given by (9). In these numerical simulations we considered $\beta_1 = 2.7$ and $\beta_2 = 0.03$, corresponding to $R_1 = 0.62632$ and $R_2 = 0.55077$, while the rest of the parameters take the values in Table 1.

Figure 3 shows that, for $R_0 > 1$, the syndemic equilibrium Σ^{*} exists. We considered different initial conditions for the state variables of system (4) in a neighborhood of (19), $\beta_1 = 6$ and $\beta_2 = 0.1$, corresponding to $R_1 = 1.39239$ and $R_2 = 1.83593$, and the rest of the parameters take the values in

Table 1: Parameters of the TB-HIV/AIDS model (4).

Symbol	Value	References	Symbol	Value	References
Λ	714		τ_4	$1\ \text{yr}^{-1}$	
μ	$1/70\ \text{yr}^{-1}$		ρ_1	$0.1\ \text{yr}^{-1}$	[10, 11]
β_1	Variable		ρ_2	$0.25\ \text{yr}^{-1}$	
β_2	Variable		ρ_3	$0.125\ \text{yr}^{-1}$	
β_1'	0.9		α_1	$0.33\ \text{yr}^{-1}$	[6]
β_2'	1.1		α_2	$0.33\ \text{yr}^{-1}$	
k_1	1	[12]	ψ	1.07	
k_2	$1.3k_1$	[13]	d_T	$1/8\ \text{yr}^{-1}$	
τ_1	$1\ \text{yr}^{-1}$	[12]	d_A	$0.3\ \text{yr}^{-1}$	
τ_2	$2\ \text{yr}^{-1}$	[12]	d_{TA}	$0.33\ \text{yr}^{-1}$	
τ_3	$2\ \text{yr}^{-1}$		η	1.02	
δ	1.03				

Table 2: Effect of β_1 on $I_T^{\diamond}$ and R_1.

β_1	4.3	6	10	15	50
R_1	0.99788	1.39239	2.32065	3.48097	11.60326
$I_T^{\diamond}$	0.00397	903.93492	2206.57268	2870.72755	3804.50589

Table 3: Effect of β_2 on $I_H^{\star}$, $A^{\star}$, and R_2.

β_2	0.051	0.055	0.07	0.09	0.99
R_2	0.93669	1.01016	1.28566	1.65299	1.81829
$I_H^{\star}$	0.01708	135.73817	2516.54721	4472.84980	4930.48696
$A^{\star}$	0.00266	21.07182	390.59491	694.23361	765.26396

Table 1. We observe that the state variables converge to Σ^* when $t \to \infty$. In this case, Σ^* is given by

$$\begin{aligned}\Sigma^* &= \left(S^*, L_T^*, I_T^*, R_T^*, I_H^*, A^*, L_{TH}^*, I_{TH}^*, R_{TH}^*, A_T^*\right)\\ &= (4766.84, 2019.66, 943.06, 28621.89, 362.66, 56.29,\\ &\quad 31.39, 55.15, 495.68, 112.33)\,.\end{aligned} \tag{20}$$

5.2. Treatment Impact on TB-HIV/AIDS Coinfection. Consider $\beta_1 = 13$ and $\beta_2 = 0.06$, while the rest of the parameters take the values of Table 1. Figure 4 shows the impact of treating the individuals with active and latent TB on the number of individuals coinfected with TB-HIV/AIDS. The treatment of individuals with only TB, I_T and L_T, has a positive impact on the reduction of the number of individuals coinfected with TB-HIV/AIDS. Moreover, the number of individuals that suffered from disease (TB and AIDS) induced death is higher when individuals with TB-single infection are not treated. In this case, the total population at the end of 20 years is around 10509 and, in the case where individuals with only TB are treated, the total population at the end of 20 years is around 29758 individuals. In Figure 5, we assume that there are no disease induced deaths; that is, $d_T = d_A = d_{TA} = 0$. The impact of treating individuals with only TB on the reduction of the number of coinfected individuals is more evident.

Figure 6 illustrates the case where we compare the number of individuals coinfected with TB-HIV/AIDS when individuals with only AIDS symptoms A_T are or are not treated. We observe that treating this class of individuals is important for the reduction of the number of individuals that become coinfected, with special attention to the individuals that have AIDS symptoms and TB infection. In Figure 7, we considered that there are no disease induced deaths ($d_T = d_A = d_{TA} = 0$). It is crucial that TB-infected individuals (in the latent and active stage), which are also HIV-positive, take anti-TB drugs, since they can recover from TB. We analyze the impact of treating TB-HIV/AIDS coinfected individuals L_{TH}, I_{TH}, and A_T on the reduction of the number of individuals coinfection. If anti-TB drugs are supplied, then latent and active TB individuals with HIV can recover and pass to the class R_{TH} (the number of individuals in the class R_{TH} tends to zero when TB is not treated). In Figure 8, we observe that, after 7 years, the number of individuals infected with active TB and HIV, in the case without treatment, becomes lower than in the case with treatment. This is due to the fact that coinfection precipitates AIDS symptoms.

Appendices

A. Computation of R_0

The basic reproduction number represents the expected average number of new infections produced by a single infectious

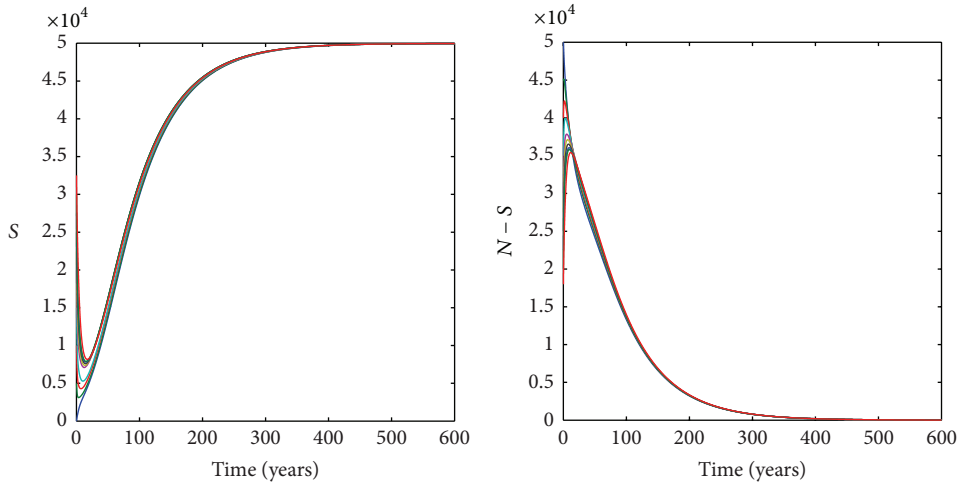

Figure 2: Stability of the disease-free equilibrium (9).

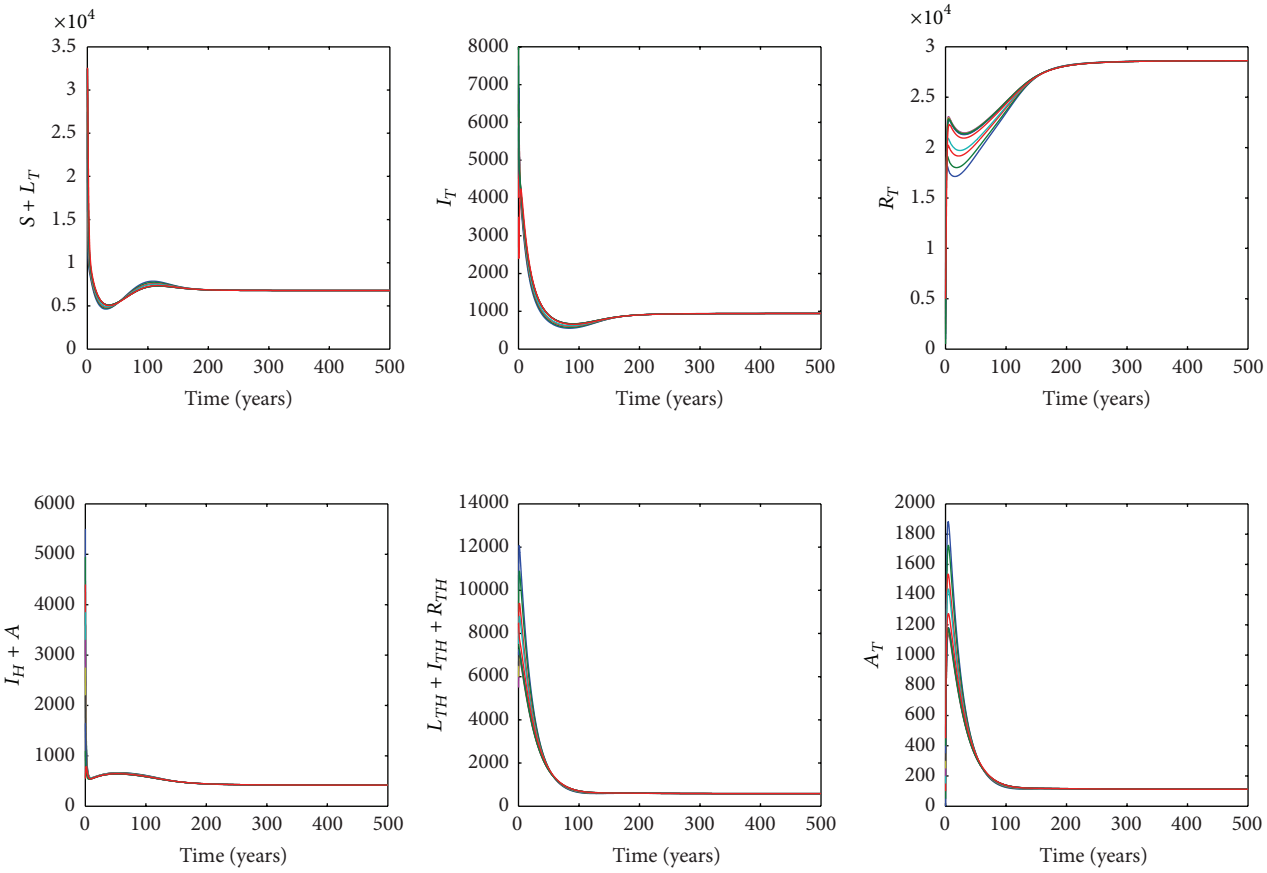

Figure 3: Stability of the syndemic equilibrium Σ^*.

individual when in contact with a completely susceptible population [16]. Following [16], the basic reproduction number R_0 is obtained as the spectral radius of the matrix $F \cdot V^{-1}$ at the disease-free equilibrium Σ_0, given by (9), with $F = [F_1 \quad F_2]$,

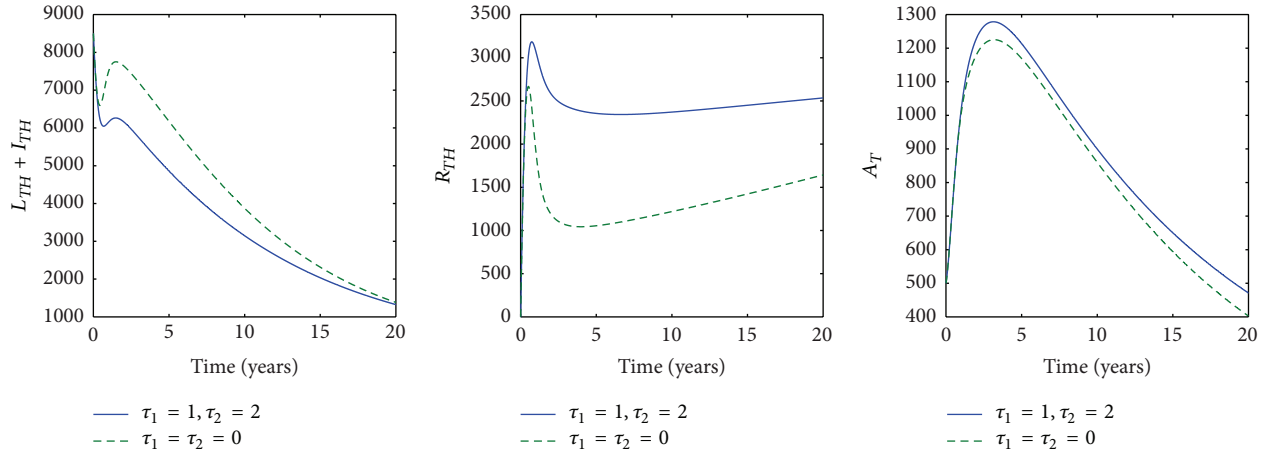

Figure 4: Impact of TB treatment on single-infected individuals with disease induced death.

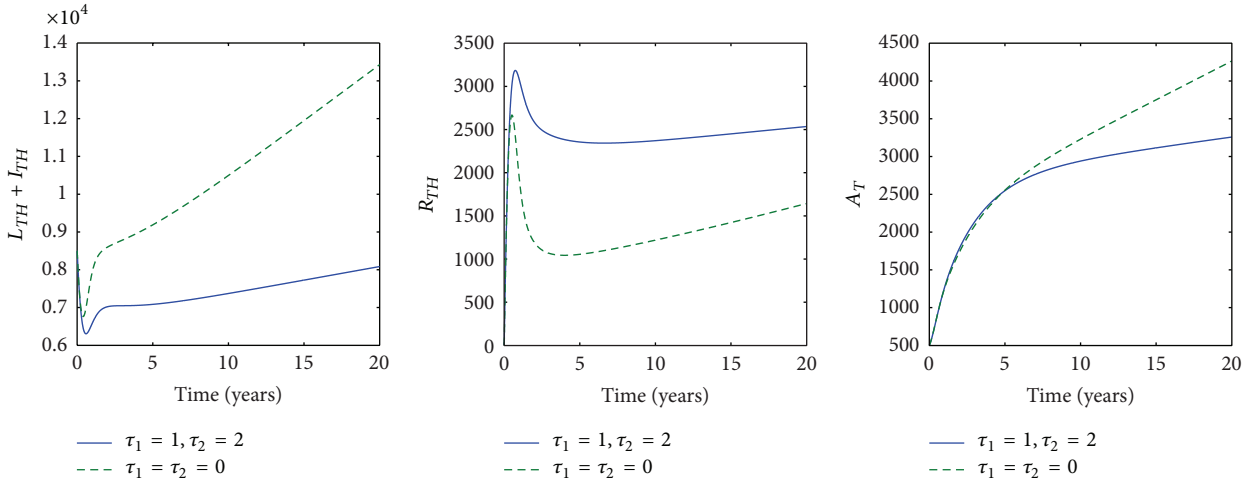

Figure 5: Impact of TB treatment on single-infected individuals with no disease induced death.

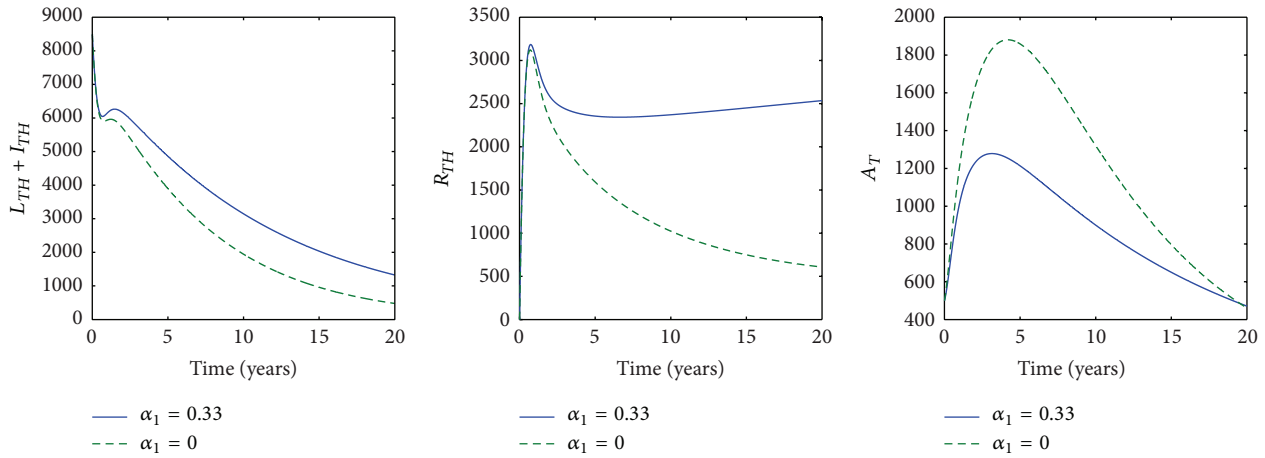

Figure 6: Impact of AIDS treatment on single-infected individuals with disease induced death.

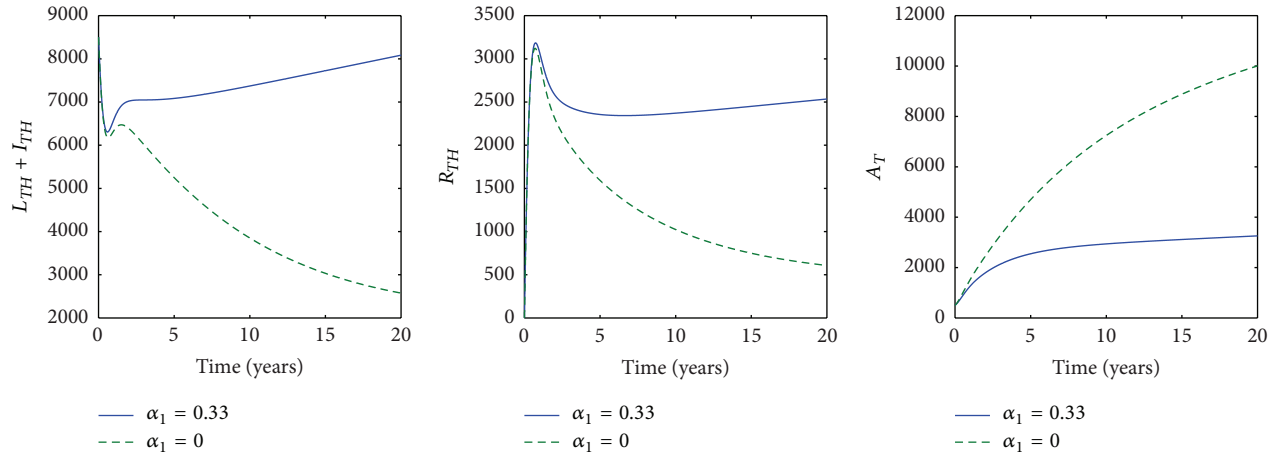

Figure 7: Impact of AIDS treatment on single-infected individuals with no disease induced death.

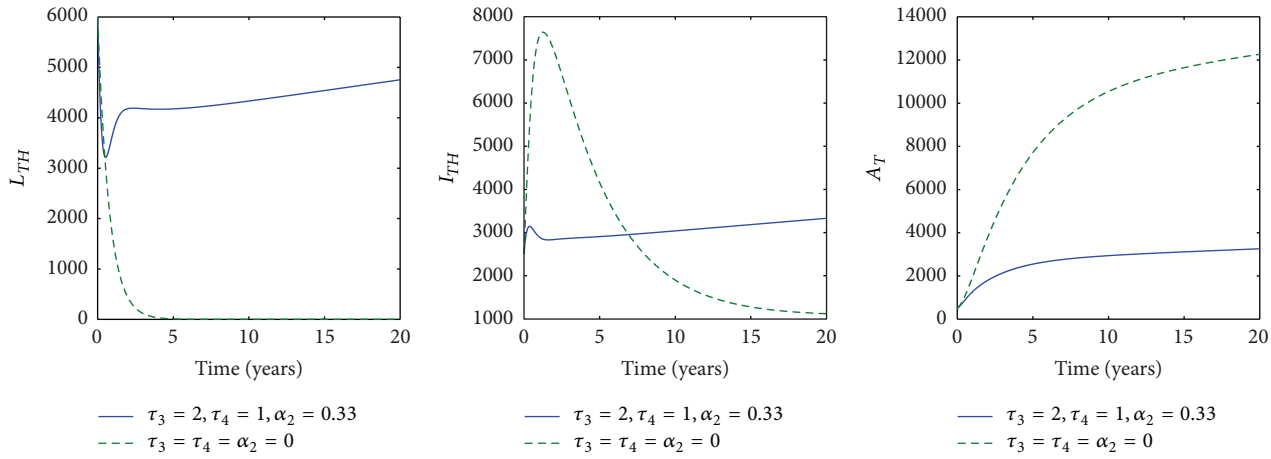

Figure 8: Impact of TB and AIDS treatment on coinfected individuals with no disease induced death.

$$F_1 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ \lambda_T & 0 & \dfrac{\beta_1 S}{N} + \dfrac{\beta_1' \beta_1 R_T}{N} & \beta_1' \lambda_T & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \lambda_H & 0 & 0 & \lambda_H & \dfrac{\beta_2 S}{N} + \dfrac{\beta_2 R_T}{N} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \dfrac{\beta_2' \beta_1 R_{TH}}{N} & 0 & 0 \\ 0 & 0 & \delta\lambda_H + \dfrac{\psi\beta_1 I_H}{N} & 0 & \dfrac{\delta\beta_2 I_T}{N} + \psi\lambda_T \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$F_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_1 S}{N} + \frac{\beta_1' \beta_1 R_T}{N} & 0 & \frac{\beta_1 S}{N} + \frac{\beta_1' \beta_1 R_T}{N} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_2 \eta S}{N} + \frac{\beta_2 \eta R_T}{N} & \frac{\beta_2 S}{N} + \frac{\beta_2 R_T}{N} & \frac{\beta_2 S}{N} + \frac{\beta_2 R_T}{N} & \frac{\beta_2 S}{N} + \frac{\beta_2 R_T}{N} & \frac{\beta_2 S \eta}{N} + \frac{R_T \beta_2 \eta}{N} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_2' \beta 1 R_{TH}}{N} & \beta_2' \lambda_T & \frac{\beta_2' \beta_1 R_{TH}}{N} \\ \frac{\delta \beta_2 \eta I_T}{N} & \frac{\delta \beta_2 I_T}{N} & \frac{\delta \beta_2 I_T}{N} + \frac{\psi \beta_1 I_H}{N} & \frac{\delta \beta_2 I_T}{N} & \frac{\delta \beta_2 \eta I_T}{N} + \frac{\psi \beta_1 I_H}{N} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{A.1}$$

and $V = [V_1 \quad V_2]$ with

$$V_1 = \begin{bmatrix} \lambda_T + \lambda_H + \mu & 0 & \frac{\beta_1 S}{N} & 0 & \frac{\beta_2 S}{N} \\ 0 & k_1 \tau_1 + \mu & 0 & 0 & 0 \\ 0 & -k_1 & \tau_2 + \delta \lambda_H + \mu + d_T & 0 & \frac{\delta \beta_2 I_T}{N} \\ 0 & -\tau_1 & -\tau_2 + \frac{\beta_1' \beta_1 R_T}{N} & \beta_1' \lambda_T + \lambda_H + \mu & \frac{\beta_2 R_T}{N} \\ 0 & 0 & \frac{\psi \beta_1 I_H}{N} & 0 & \rho_1 + \psi \lambda_T + \mu \\ 0 & 0 & 0 & 0 & -\rho_1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_2' \beta_1 R_{TH}}{N} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V_2 = \begin{bmatrix} \frac{\beta_2 \eta S}{N} & \frac{\beta_2 S}{N} & \frac{\beta_1 S}{N} + \frac{\beta_2 S}{N} & \frac{\beta_2 S}{N} & \frac{\beta_1 S}{N} + \frac{\beta_2 S \eta}{N} \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\delta \beta_2 \eta I_T}{N} & \frac{\delta \beta_2 I_T}{N} & \frac{\delta \beta_2 I_T}{N} & \frac{\delta \beta_2 I_T}{N} & \frac{\delta \beta_2 \eta I_T}{N} \\ \frac{\beta_2 \eta R_T}{N} & \frac{\beta_2 R_T}{N} & \left(\frac{\beta_1' \beta_1}{N} + \frac{\beta_2}{N} \right) R_T & \frac{\beta_2 R_T}{N} & \left(\frac{\beta_1' \beta_1}{N} + \frac{\beta_2 \eta}{N} \right) R_T \\ -\alpha_1 & 0 & \frac{\psi \beta_1 I_H}{N} & 0 & \frac{\psi \beta_1 I_H}{N} \\ \alpha_1 + \mu + d_A & 0 & 0 & 0 & 0 \\ 0 & k_2 + \tau_4 + \mu & 0 & 0 & 0 \\ 0 & -k_2 & \rho_2 + \tau_3 + \mu + d_T & 0 & -\alpha_2 \\ 0 & -\tau_4 & -\tau_3 + \frac{\beta_2' \beta_1 R_{TH}}{N} & \beta_2' \lambda_T + \rho_3 + \mu & \frac{\beta_2' \beta_1 R_{TH}}{N} \\ 0 & 0 & -\rho_2 & -\rho_3 & \alpha_2 + d_{TA} + \mu \end{bmatrix}. \tag{A.2}$$

The dominant eigenvalues of the matrix $F \cdot V^{-1}$ are

$$R_1 = \frac{\Lambda}{N\mu}\left(\frac{\beta_1}{d_T+\mu+\tau_2}\right)\left(\frac{k_1}{k_1+\tau_1+\mu}\right),$$
$$R_2 = \frac{\Lambda}{N\mu}\beta_2\left(\frac{\mu+\alpha_1+d_A+\eta\rho_1}{\mu\alpha_1+(\mu+\rho_1)(\mu+d_A)}\right). \tag{A.3}$$

Thus, the basic reproduction number R_0 of model (4) is given by

$$R_0 = \max\{R_1, R_2\}. \tag{A.4}$$

Note that R_1 is the basic reproduction number of model (4) with $I_T = A = L_{TH} = I_{TH} = R_{TH} = A_T = 0$ (only TB model), and R_2 is the basic reproduction number of model (4) with $L_T = I_T = R_T = L_{TH} = I_{TH} = R_{TH} = A_T = 0$ (only HIV-AIDS model).

B. Proof of Theorem 2

In this Appendix, we provide details of the proof of Theorem 2.

Local Asymptotical Stability of the Disease-Free Equilibrium Σ_0. Following Theorem 2 of [16], the disease-free equilibrium, Σ_0, is locally asymptotically stable if all the eigenvalues of the Jacobian matrix of the system (4), here denoted by $M_T(\Sigma_0)$, computed at the disease-free equilibrium Σ_0, given by (9), have negative real parts.

The Jacobian matrix of the system (4) at disease-free equilibrium Σ_0 is given by

$$M_T(\Sigma_0) = \left[M_{T1}(\Sigma_0) \;\; M_{T_2}(\Sigma_0)\right] \tag{B.1}$$

with

$$M_{T1}(\Sigma_0) = \begin{bmatrix} -\mu & 0 & -\frac{\beta_1\Lambda}{\mu N} & 0 & -\frac{\beta_2\Lambda}{\mu N} \\ 0 & -d_1 & \frac{\beta_1\Lambda}{\mu N} & 0 & 0 \\ 0 & k_1 & -d_2 & 0 & 0 \\ 0 & \tau_1 & \tau_2 & -\mu & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_2\Lambda}{\mu N} - d_3 \\ 0 & 0 & 0 & 0 & \rho_1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$M_{T2}(\Sigma_0) = \begin{bmatrix} -\frac{\beta_2\eta\Lambda}{\mu N} & -\frac{\beta_2\Lambda}{\mu N} & -\frac{\beta_1\Lambda}{\mu N} - \frac{\beta_2\Lambda}{\mu N} & -\frac{\beta_2\Lambda}{\mu N} & -\frac{\beta_1\Lambda}{\mu N} - \frac{\beta_2\eta\Lambda}{\mu N} \\ 0 & 0 & \frac{\beta_1\Lambda}{\mu N} & 0 & \frac{\beta_1\Lambda}{\mu N} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_2\eta\Lambda}{\mu N} + \alpha_1 & \frac{\beta_2\Lambda}{\mu N} & \frac{\beta_2\Lambda}{\mu N} & \frac{\beta_2\Lambda}{\mu N} & \frac{\beta_2\eta\Lambda}{\mu N} \\ -d_4 & 0 & 0 & 0 & 0 \\ 0 & -d_5 & 0 & 0 & 0 \\ 0 & k_2 & -d_6 & 0 & \alpha_2 \\ 0 & \tau_4 & \tau_3 & -d_7 & 0 \\ 0 & 0 & \rho_2 & \rho_3 & -d_8 \end{bmatrix}, \tag{B.2}$$

where $d_1 = k_1 + \tau_1 + \mu$; $d_2 = \tau_2 + \mu + d_T$; $d_3 = \rho_1 + \mu$; $d_4 = \alpha_1 + \mu + d_A$; $d_5 = k_2 + \mu + \tau_4$; $d_6 = \rho_2 + \tau_3 + \mu + d_T$; $d_7 = \rho_3 + \mu$; $d_8 = \alpha_2 + d_{TA} + \mu$. One has

$$\begin{aligned}
&\operatorname{trace}\left[M_T\left(\Sigma_0\right)\right] \\
&\quad = -2\mu - \left(d_1 + d_2 + d_3 + d_4 + d_5 + d_6 + d_7 + d_8\right) < 0, \\
&\det\left[M_T\left(\Sigma_0\right)\right] \\
&\quad = \frac{1}{N^2}\left(d_5\left(d_6 d_7 + d_T\left(\alpha_2 + \mu\right)d_7 + \alpha_2\mu d_6 + d_T d_{TA} d_7\right)\right. \\
&\qquad \times \left(N\mu\left(\alpha_1\mu + \left(\mu + \rho_1\right)\left(\mu + d_A\right)\right)\right. \\
&\qquad\quad \left.\left. - \beta_2\Lambda\left(\alpha_1 + \mu + d_A + \rho_1\eta\right)\right)\right. \\
&\qquad \left. \times \left(N\mu\left(d_T + \mu + \tau_2\right)\left(k_1 + \tau_1 + \mu\right) - k_1\beta_1\Lambda\right) > 0\right.
\end{aligned} \tag{B.3}$$

for

$$\begin{aligned}
R_1 &= \frac{\Lambda}{N\mu}\left(\frac{\beta_1}{d_T + \mu + \tau_2}\right)\left(\frac{k_1}{k_1 + \tau_1 + \mu}\right) < 1, \\
R_2 &= \frac{\Lambda}{N\mu}\beta_2\left(\frac{\mu + \alpha_1 + d_A + \eta\rho_1}{\mu\alpha_1 + \left(\mu + \rho_1\right)\left(\mu + d_A\right)}\right) < 1.
\end{aligned} \tag{B.4}$$

We have just proved that the disease-free equilibrium Σ_0 of model (4) is locally asymptotically stable if $R_0 < 1$ and unstable if either $R_i > 1$, $i = 1, 2$.

Global Asymptotical Stability of the Disease-Free Equilibrium Σ_0. For convenience, let us rewrite the model system (4) as

$$\begin{aligned}
\frac{dX}{dt} &= F\left(X, Z\right), \\
\frac{dZ}{dt} &= G\left(X, Z\right), \qquad G\left(X, 0\right) = 0,
\end{aligned} \tag{B.5}$$

where $X = (S, R_T)$ and $Z = (L_T, I_T, I_H, A, L_{TH}, I_{TH}, R_{TH}, A_T)$, with $X \in \mathbb{R}_+^2$ denoting (its components) the number of uninfected individuals and $Z \in \mathbb{R}_+^8$ denoting (its components) the number of infected individuals including the latent and infectious.

The disease-free equilibrium is denoted by

$$E_0 = \left(X_0, 0\right), \quad \text{where } X_0 = \left(\frac{\Lambda}{\mu}, 0\right). \tag{B.6}$$

Following [6], if

(H1) E_0 is globally asymptotically stable for $dX/dt = F(X, 0)$,

(H2) $\widehat{G}(X, Z) \geqslant 0$ for $(X, Z) \in \Omega$, where $G(X, Z) = AZ - \widehat{G}(X, Z)$, $A = D_Z G(E_0, 0)$ is a Metzler matrix, and Ω is given by (6),

then the fixed point $E_0 = (X_0, 0)$ is a globally asymptotically stable equilibrium of system (B.5). We have

$$\begin{aligned}
\frac{dX}{dt} = F\left(X, Z\right) &= \begin{bmatrix} \Lambda - \lambda_T S - \lambda_H S - \mu S \\ \tau_1 L_T + \tau_2 I_T - \left(\beta_1'\lambda_T + \lambda_H + \mu\right)R_T \end{bmatrix}, \\
F\left(X, 0\right) &= \begin{bmatrix} \Lambda - \mu S \\ -\mu R_T \end{bmatrix}, \\
\frac{dZ}{dt} &= G\left(X, Z\right) \\
&= \begin{bmatrix} \lambda_T S + \beta_1'\lambda_T R_T - \left(k_1 + \tau_1 + \mu\right)L_T \\ k_1 L_T - \left(\tau_2 + d_T + \mu + \delta\lambda_H\right)I_T \\ \lambda_H S - \left(\rho_1 + \psi\lambda_T + \mu\right)I_H + \alpha_1 A + \lambda_H R_T \\ \rho_1 I_H - \alpha_1 A - \left(\mu + d_A\right)A \\ \beta_2'\lambda_T R_{TH} - \left(k_2 + \tau_4 + \mu\right)L_{TH} \\ \delta\lambda_H I_T + \psi\lambda_T I_H + \alpha_2 A_T + k_2 L_{TH} - \left(\tau_3 + \rho_2 + \mu + d_T\right)I_{TH} \\ \tau_3 I_{TH} + \tau_4 L_{TH} - \left(\beta_2'\lambda_T + \rho_3 + \mu\right)R_{TH} \\ \rho_2 I_{TH} + \rho_3 R_{TH} - \left(\alpha_2 + \mu + d_{TA}\right)A_T \end{bmatrix},
\end{aligned} \tag{B.7}$$

and $G(X, 0) = 0$. Thus,

$$\begin{aligned}
\frac{dX}{dt} &= F\left(X, 0\right) = \begin{bmatrix} \Lambda - \mu S \\ -\mu R_T \end{bmatrix}, \\
A &= D_Z G\left(X_0, 0\right) = \begin{bmatrix} D_1 & D_2 \end{bmatrix}
\end{aligned} \tag{B.8}$$

with

$$D_1 = \begin{bmatrix} -k_1 - \tau_1 - \mu & \frac{\beta_1 \Lambda}{\mu N} & 0 & 0 \\ k_1 & -\tau_2 - \mu - d_T & 0 & 0 \\ 0 & 0 & \frac{\beta_2 \Lambda}{\mu N} - \rho_1 - \mu & \frac{\beta_2 \eta \Lambda}{\mu N} + \alpha_1 \\ 0 & 0 & \rho_1 & -\alpha_1 - \mu - d_A \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$D_2 = \begin{bmatrix} 0 & \frac{\beta_1 \Lambda}{\mu N} & 0 & \frac{\beta_1 \Lambda}{\mu N} \\ 0 & 0 & 0 & 0 \\ \frac{\beta_2 \Lambda}{\mu N} & \frac{\beta_2 \Lambda}{\mu N} & \frac{\beta_2 \Lambda}{\mu N} & \frac{\beta_2 \eta \Lambda}{\mu N} \\ 0 & 0 & 0 & 0 \\ -k_2 - \tau_4 - \mu & 0 & 0 & 0 \\ k_2 & -\rho_2 - \tau_3 - \mu - d_T & 0 & \alpha_2 \\ \tau_4 & \tau_3 & -\rho_3 - \mu & 0 \\ 0 & \rho_2 & \rho_3 & -\alpha_2 - d_{TA} - \mu \end{bmatrix},$$

$$\widehat{G}(X, Z) = \begin{bmatrix} \lambda_T \left(\frac{\Lambda}{\mu} - S - \beta_1' R_T \right) \\ -\delta \lambda_H I_T \\ \lambda_H \left(\frac{\Lambda}{\mu} - S - R_T - \psi I_H \right) \\ 0 \\ -\beta_2' \lambda_T R_{TH} \\ -\left(\delta \lambda_H I_T + \psi \lambda_T I_H \right) \\ \beta_2' \lambda_T R_{TH} \\ 0 \end{bmatrix}. \tag{B.9}$$

From (B.9) the condition (H2) is not satisfied, since $\widehat{G}(X, Z) \geqslant 0$ is not true. Therefore, the disease-free equilibrium E_0 may not be globally asymptotically stable. Following [17], the backward bifurcation occurs at $R_0 = 1$ and the double endemic equilibria can be supported for $R_c < R_0 < 1$, where R_c is a positive constant.

Existence and Stability of HIV-AIDS Free Equilibrium Σ_T. The expressions for $S^\diamond$, $L_T^\diamond$, $I_T^\diamond$, and $R_T^\diamond$ are obtained if we consider a submodel of (4) for which $I_H = A = L_{TH} = I_{TH} = R_{TH} = A_T = 0$ and the total population N is given by $N_T = S + L_T + I_T + R_T$. The basic reproduction number of this submodel is given by R_1 (11). The existence, uniqueness, and local asymptotic stability of Σ_T are proven in [12, Theorem 1].

Existence and Stability of TB-Free Equilibrium Σ_H. To prove the existence of Σ_T, consider the submodel of (4) for which $L_T = I_T = R_T = L_{TH} = I_{TH} = R_{TH} = A_T = 0$ and the total population N_H is given by $N_H = S + I_H + A$. The equations of this submodel are

$$\begin{aligned} \dot{S}(t) &= \Lambda - \lambda_H S(t) - \mu S(t), \\ \dot{I}_H(t) &= \lambda_H S(t) - (\rho_1 + \mu) I_H(t) + \alpha_1 A(t), \\ \dot{A}(t) &= \rho_1 I_H(t) - \alpha_1 A(t) - (\mu + d_A) A, \end{aligned} \tag{B.10}$$

where $\lambda_H = \beta_2((I_H + \eta A)/N_H)$. Setting the right-hand sides of submodel (B.10) to zero, we obtain the endemic equilibrium $\Sigma_H^\star = (S^\star, I_H^\star, A^\star)$ given by

$$S^\star = \frac{\Lambda}{\mu R_2},$$

$$I_H^\star = (R_2 - 1)\frac{\mu N_H(\alpha_1 + d_A + \mu)}{\beta_2(\alpha_1 + d_A + \mu + \eta\rho_1)},$$
$$A^\star = (R_2 - 1)\frac{\rho_1 \mu N_H}{\beta_2(\alpha_1 + d_A + \mu + \eta\rho_1)}, \tag{B.11}$$

where $I_H^\star > 0$ and $A^\star > 0$, whenever $R_2 > 1$.

In what follows we prove the local asymptotic stability of the endemic equilibrium $\Sigma_H^\star$, using the center manifold theory [18], as described in [19, Theorem 4.1] (see also [16]), considering ART treatment. The basic reproduction number of this submodel R_2 is given by (16). Choose bifurcation parameter, β^*, by solving for β_2 from $R_2 = 1$:

$$\beta^* = \frac{\mu\alpha_1 + (\mu + \rho_1)(\mu + d_A)}{\alpha + d_A + \mu + \eta\rho}. \tag{B.12}$$

Submodel (B.10) has a disease-free equilibrium given by $\Sigma_{H0}^* = (x_{10}, x_{20}, x_{30}) = (\Lambda/\mu, 0, 0)$.

The Jacobian of the system (B.10), evaluated at Σ_{H0}^* and with $\beta_2 = \beta^*$, is given by

$$J(\Sigma_{H0}^*) = \begin{bmatrix} -\mu & -\beta_2 & -\beta_2\eta \\ 0 & \beta_2 - \rho - \mu & \beta_2\eta + \alpha \\ 0 & \rho & -\alpha - d_A - \mu \end{bmatrix}. \tag{B.13}$$

The eigenvalues of the linearized system (B.13) are

$$\lambda_1 = 0, \qquad \lambda_2 = -\mu,$$
$$\lambda_3 = -\left(\eta\rho\left(2\mu^2 + \rho + d_A + \alpha\right) + d_A(2\alpha + 2\mu + d_A) + \rho\alpha + (\mu + \alpha)^2\right)(\alpha + d_A + \mu + \eta\rho)^{-1}. \tag{B.14}$$

We observe that there is a simple eigenvalue with zero real part and the other two eigenvalues have negative real part. Thus, the system (B.10), with $\beta_2 = \beta^*$, has a hyperbolic equilibrium point and the center manifold theory [18] can be used to analyze the dynamics of submodel (B.10) near $\beta_2 = \beta^*$.

The Jacobian $J(\Sigma_{H0}^*)$ at $\beta_2 = \beta^*$ has a right eigenvector (associated with the zero eigenvalue) given by $w = [w_1, w_2, w_3]^T$, where

$$w_1 = -\frac{(\mu\alpha_1 + (\mu + \rho_1)(\mu + d_A))w_3}{\rho_1\mu},$$
$$w_2 = \frac{(\alpha_1 + d_A + \mu)w_3}{\rho_1}, \tag{B.15}$$
$$w_3 = w_3 > 0.$$

Further, $J(\Sigma_{H0}^*)$ for $\beta_2 = \beta^*$ has a left eigenvector $v = [v_1, v_2, v_3]$ (associated with the zero eigenvalue), where

$$v_1 = 0,$$
$$v_2 = \frac{v_3(\alpha_1 + d_A + \mu + \eta\rho_1)}{\alpha_1 + \eta\rho_1 + \mu\eta}, \tag{B.16}$$
$$v_3 = v_3 > 0.$$

To apply Theorem 4.1 in [19] it is convenient to let f_k represent the right-hand side of the kth equation of the system (B.10) and let x_k be the state variable whose derivative is given by the kth equation for $k = 1, 2, 3$. The local stability near the bifurcation point $\beta_2 = \beta^*$ is then determined by the signs of two associated constants, denoted by a and b, defined (respectively) by

$$a = \sum_{k,i,j=1}^{3} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$
$$b = \sum_{k,i=1}^{3} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \tag{B.17}$$

with $\phi = \beta_2 - \beta^*$.

For the system (B.10), the associated partial derivatives at the disease-free equilibrium Σ_{H0} are given by

$$\frac{\partial^2 f_1}{\partial x_2^2} = \frac{2\beta^*\mu}{\Lambda}, \qquad \frac{\partial^2 f_1}{\partial x_2 \partial x_3} = \frac{\beta^*\mu(1+\eta)}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_3^2} = \frac{2\beta^*\mu\eta}{\Lambda}, \qquad \frac{\partial^2 f_2}{\partial x_2^2} = \frac{-2\beta^*\mu}{\Lambda}, \tag{B.18}$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{-\beta^*\mu(1+\eta)}{\Lambda}, \qquad \frac{\partial^2 f_2}{\partial x_3^2} = \frac{-2\beta^*\mu\eta}{\Lambda}.$$

It follows from the above expressions that

$$a = -v_3 w_3^2 \beta^* \mu (k_1 + \mu + \eta\rho_1) \times \left(2k_1^2 + 4\mu k_1 + 2\mu^2 + \rho_1(\alpha_1 + \eta(\alpha_1 + \mu + 2\rho_1) + d_A(1+\eta) + \mu)\right) \times \left(\rho_1^2 \Lambda(\alpha_1 + \eta\rho_1 + \mu\eta)\right)^{-1} < 0 \tag{B.19}$$

with $k_1 = \alpha_1 + d_A$.

For the sign of b, it can be shown that the associated nonvanishing partial derivatives are

$$\frac{\partial^2 f_1}{\partial x_2 \partial \beta^*} = -1, \qquad \frac{\partial^2 f_1}{\partial x_3 \partial \beta^*} = -\eta,$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta^*} = 1, \qquad \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = \eta. \tag{B.20}$$

It also follows from the above expressions that

$$b = \frac{v_3 w_3 (k_1 + \mu + \eta\rho_1)(k_1 + \mu)}{(\alpha_1 + \eta\rho_1 + \mu\eta)\rho_1} + \frac{\eta v_3 w_3 (k_1 + \mu + \eta\rho_1)}{\alpha_1 + \eta\rho_1 + \mu\eta} > 0. \tag{B.21}$$

Thus, $a < 0$ and $b > 0$. Using Theorem 4.1 of [19], the endemic equilibrium $\Sigma_H^\star$ is locally asymptotically stable for R_2 near 1.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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